

**U.S.S.N. 10/613,474
Pandey et al.
Preliminary Amendment**

IN THE SPECIFICATION:

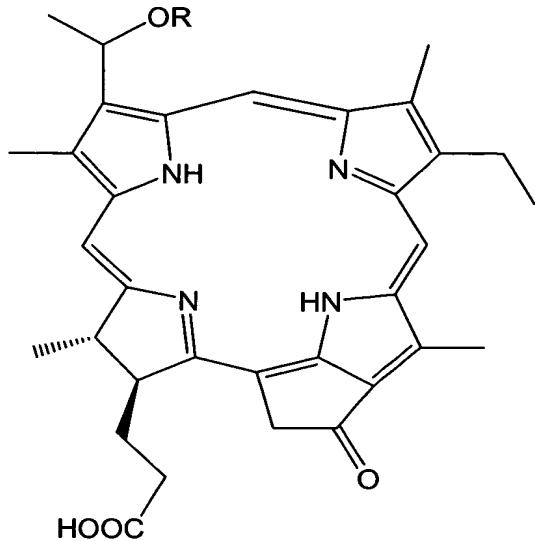
Please amend the specification as follows:

Please replace the paragraph on page 2, lines 11-14 of the Specification as follows:

Provided herein is a synthetic process for the preparation of hexyloxy pyropheophorbide a and related compounds. The process is suitable [of] for large scale (*i.e.*, multigram to multi-kilogram or more) production of such compounds.

Please replace the paragraph on page 4, line 9 through page 5, line 7 of the specification as follows:

As used herein, "ether analogs of pyropheophorbide a" refers to compounds of the general formula:

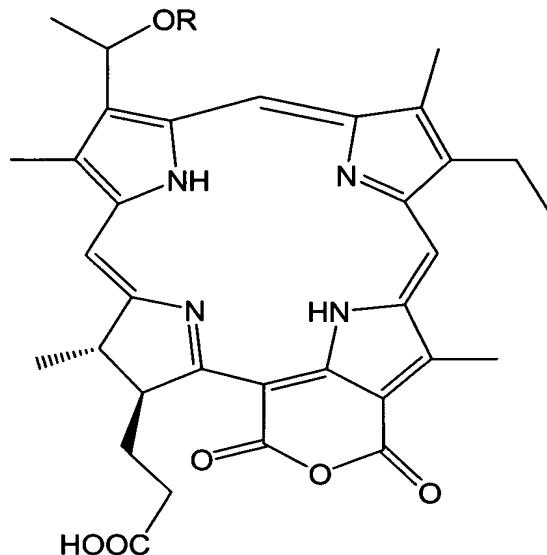


where R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

Please replace the paragraph on page 6, lines 3-11 of the Specification as follows:

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As used herein, "ether analogs of purpurin-18" refers to compounds of the general formula:

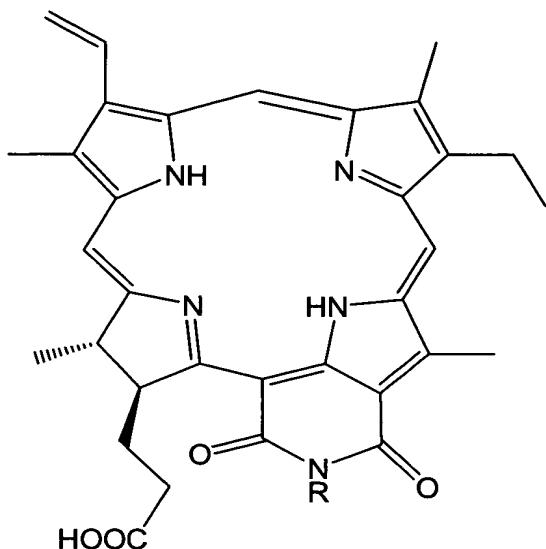


where R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

Please replace the paragraph on page 6, line 12 through page 7, line 7 of the Specification as follows:

As used herein, a "purpurinimide" is a compound of the general formula:

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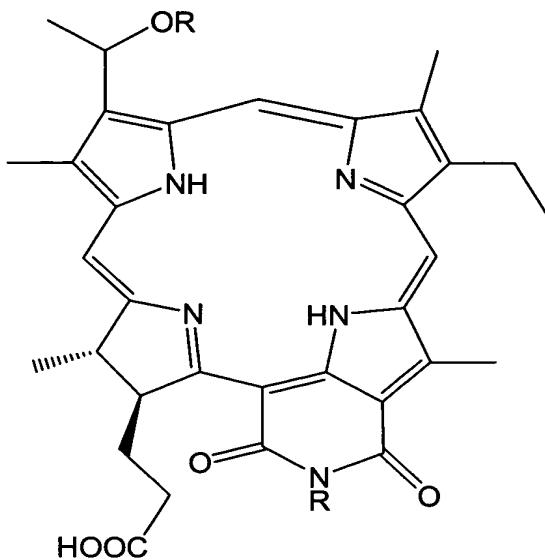


where R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

Please replace the paragraph on page 7, line 8 through page 8, line 4 of the Specification as follows:

As used herein, "ether analogs of purpurinimides" refers to compounds of the general formula:

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where each R is independently alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl, and is unsubstituted or substituted with one or more substituents, in one embodiment one to five substituents, in another embodiment one, two or three substituents, each independently selected from halo, pseudohalo, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, hydroxy, alkoxy, aryloxy, carboxy, aralkoxy, sulfones, amines, amides and sulfonamides.

Please replace the paragraph on page 11, lines 10-22 of the Specification as follows:

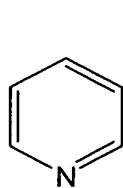
The process provided herein, depicted below, avoids a number of shortcomings of the prior art by resorting to another source as the raw material. Chlorin e₆ trimethyl ester undergoes a Dieckmann Condensation to form the additional[[,]] exocyclic ring, sometimes called an "E-ring", [[that]] which is present in the pheophorbides, and chlorophyll itself for that matter. See, e.g., Schaefer, J.P.; Bloomfield, J.J. *Org. React.* **1967**, *15*, 1-203; and Davis, B.R.; Garrett, P.J. *Comp. Org. Syn.* **1991**, *2*, 806-829. This reaction has traditionally been performed in aromatic solvents, originally benzene, but later toluene and others for safety reasons. In the case of chlorin e₆ and compounds like it, pyridine has been used for this purpose. See, e.g., Smith, K.M.; Bisset, G.M.F.; Bushell, M.J. *J. Org. Chem.* **1980**, *45*, 2218-2224. These workers did not use chlorin e₆ itself, but a similar

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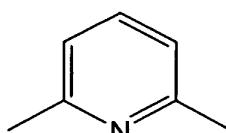
compound in which a methyl group substituent was present at position 5, the δ "meso" position.

Please replace the paragraph on page 11, line 24 through page 12, line 14 of the Specification as follows:

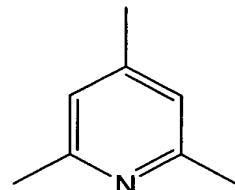
In order to improve the performance of this reaction, the pyridine was replaced with a more substituted analog in order to raise the boiling point of the reaction mixture. Thus, collidine, also called *sym*-collidine (for symmetrical, see below) or 2,4,6-trimethylpyridine, was used. Other basic aromatic solvents, including but not limited to 2,6-lutidine, could also be used. In this way the temperature of reflux of the reaction mixture is altered - the boiling point of pyridine is 115 °C, while that of collidine is 172 °C. By raising the temperature of the reaction mixture after completion of the Dieckmann Condensation, it is possible to bring about the subsequent thermal decarboxylation without any intervening purification or unnecessary manipulation of the reaction mixture. As a further benefit, it was found that, under the strongly basic conditions employed to carry out the Dieckmann Condensation, the methyl ester of the pheophorbide system also undergoes cleavage, thus accomplishing three chemical transformations in a single treatment.



Pyridine
Bp 115 °C
pK_a = 5.17



2,6-Lutidine
Bp 144 °C
pK_a = 6.71



sym-Collidine
Bp 172 °C
pK_a = 7.43

Basic aromatic solvents

Please replace the reaction scheme on page 13, line 1 of the Specification as follows: